Head-down bed rest impairs vagal baroreflex responses and provokes orthostatic hypotension

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CONVERTINO, VICTOR A., DONALD F. DOERR, DWAIN L. ECKBERG, JANICE M. FRITSCH, AND JOAN VERNIKOS-DANELLIS. *Head-down bed rest impairs vagal baroreflex responses and provokes orthostatic hypotension.* J. Appl. Physiol. 68(4): 1458–1464, 1990.—We studied vagally mediated carotid baroreceptor-cardiac reflexes in 11 healthy men before, during, and after 30 days of 6° head-down bed rest to test the hypothesis that baroreflex malfunction contributes to orthostatic hypotension in this model of simulated microgravity. Sigmoidal baroreflex response relationships were provoked with ramped neck pressure-suction sequences comprising pressure elevations to 40 mmHg followed by serial R-wave-triggered 15-mmHg reductions to −65 mmHg. Each R-R interval was plotted as a function of systolic pressure minus the neck chamber pressure applied during the interval. Compared with control measurements, base-line R-R intervals and the minimum, maximum, range, and maximum slope of the R-R interval-carotid pressure relationships were reduced ($P < 0.05$) from bed rest *day 12* through recovery *day 5*. Baroreflex slopes were reduced more in four subjects who fainted during standing after bed rest than in six subjects who did not faint (-1.8 ± 0.7 vs. -0.3 ± 0.3 ms/mmHg, $P < 0.05$). There was a significant linear correlation ($r = 0.70$, $P < 0.05$) between changes of baroreflex slopes from before bed rest to bed rest *day 25* and changes of systolic blood pressure during standing after bed rest. Although plasma volume declined by ~15% ($P < 0.05$), there was no significant correlation between reductions of plasma volume and changes of baroreflex responses. There were no significant changes of before and after plasma norepinephrine or epinephrine levels before and after bed rest during supine rest or sitting. We conclude that a model of microgravity, 6° head-down bed rest, significantly reduces the responsiveness and buffer capacity of vagal baroreflex-cardiac reflexes. Impaired baroreflex function appears to reduce the ability of subjects to adjust to transient changes of blood pressure during standing, and this may contribute to orthostatic intolerance.

sympathetic; blood pressure; baroreflex sensitivity; neck chamber

ASTRONAUTS who have been exposed to weightlessness have exhibited some degree of orthostatic intolerance, as manifested by reduction of mean arterial pressure and excessive cardioacceleration during standing postflight (4). Mechanisms underlying postflight orthostatic intolerance are unclear. Reduced blood volume contributes to, but probably is not a sufficient explanation for, orthostatic hypotension after spaceflight (3). Another possibility is that impaired baroreflex function after reentry impairs hemodynamic adjustments to standing.

Prolonged 6° head-down bed rest has been used to simulate hemodynamic changes that occur when humans are exposed to microgravity (3, 7, 8, 23). We conducted the present study to determine whether *1*) there are alterations in the carotid baroreceptor stimulus-cardiac reflex response relationship after prolonged 6° head-down bed rest and *2*) changes in baroreflex function (if they occur) are related to blood pressure responses during standing after bed rest. Our results indicate that impairment of vagal baroreflex function occurs during head-down bed rest and is associated with impairment of hemodynamic adjustments to standing and support the notion that baroreflex impairment may contribute to orthostatic hypotension after spaceflight.

MATERIALS AND METHODS

Subjects and measurements. Eleven healthy nonsmoking normotensive men [mean 38 ± 2 (SE) yr, range 30–45; mean height 179 ± 2 cm, range 173–188; mean weight 79 ± 2 kg, range 67–93] gave written informed consent to participate in this study, which was approved by the Kennedy Space Center Human Research Review Board. Selection of subjects was based on normal clinical results of a screening evaluation that comprised a detailed medical history, physical examination, psychological tests, complete blood count, urinalysis, 3-h glucose tolerance test, chest X-ray, resting and treadmill electrocardiograms, and a panel of blood chemistry analyses. No subject was taking medication at the time of the study. The regular daily activity levels of the subjects varied considerably, from sedentary to running 5 miles/day. During a 3-wk orientation testing period that preceded the study, all subjects were made familiar with the laboratory, the protocol, and the procedures.

Protocol. The experimental protocol was comprised of a 9-day ambulatory control period (C) followed by 30 days of 6° head-down bed rest (BR) and 5 days of recovery after bed rest (R). During bed rest, the subjects remained head-down without interruption. No conventional exercise was performed by the subjects during bed rest. However, during bed rest, three subjects received electromyostimulation to one leg for 20 min twice daily in a 3-day on 1-day off pattern as part of a supplemental

experiment on skeletal muscle. The baroreflex data of these subjects were combined with those of the remaining eight subjects, since there were no significant differences between the subject subgroups in the changes in baroreflex, plasma volume, catecholamines, or posture test responses.

During the 44-day experimental period, subjects lived 24 h/day in the Human Research Facility at NASA-Ames Research Center and followed the same controlled diet. The average daily caloric intake was 2,500–2,800 kcal (45% carbohydrate, 38% fat, 17% protein). Dietary sodium and potassium were held constant at ~120 and 60–80 meq/day, respectively. Fluid intake was ad libitum but restricted to 2,000 ml/day. The photoperiod was 16 h of light and 8 h of darkness with lights on at 0700. The 30-day bed rest period was chosen because it represents the projected minimum duration of future Space Station missions. The 6° head-down position was chosen because actual flight changes in some cardiovascular responses are closely simulated by this ground-based model (7, 23).

Each subject underwent a carotid-baroreflex test on the 4th day before bed rest (C4), on *days 1, 3, 12,* and *25* during bed rest (BR1, BR3, BR12, and BR25), and on *days 2* and *5* of recovery (R2 and R5). In addition, the subjects returned to the laboratory after 25 days of uncontrolled recovery (R30) for a final baroreflex test. During the pre-bed-rest control and post-bed-rest recovery tests, a 30-min supine rest period preceded each session.

Baroreflex stimuli. Carotid baroreflex-cardiac reflex responses were measured with a method described previously (27). Briefly, a stepping-motor-driven bellows was used to deliver a series of pressure and suction steps to a Silastic neck chamber. During held expiration, a pressure of ~40 mmHg was delivered to the chamber and held for ~5 s; then, with the next R wave, the pressure sequentially stepped to ~25, 10, −5, −20, −35, −50, and −65 mmHg and then returned to ambient pressure. Pressure steps were triggered by R waves so that neck chamber pressure changes were superimposed on naturally occurring carotid pulses. This timing was chosen so that experimental baroreceptor stimuli would be as physiological as possible. With this technique, arterial pressure changes are small (27). During each test session the stimulus sequence was repeated seven times, and the data were averaged for each subject. Unpublished data indicate that baroreceptor stimulus-sinus node response relationships, measured in this way, are highly reproducible.[1] Blood pressures were measured with a sphygmomanometer at the beginning of each test session. R-R intervals for each pressure step were plotted against carotid distending pressures (systolic pressure minus neck chamber pressure applied during the heart beat).

We used R-R intervals to characterize the pressure input-neural output relationship. This usage is based on the relationships that exist between R-R intervals and vagal-cardiac nerve activity and heart rate. R-R intervals are highly linear functions of vagal-cardiac nerve activity (17, 21). Because of this linear relationship, it is possible to use changes of R-R intervals as surrogates for changes of vagal-cardiac nerve activity and to compare responses before and after interventions such as bed rest, which alter base-line R-R intervals. Heart rates are calculated reciprocals of directly measured R-R intervals. Because the relationship between heart rate and vagal-cardiac nerve activity is curvilinear, it is extraordinarily difficult to compare responses to forcings when base-line heart rates are different. Unpublished data (D. L. Eckberg and J. M. Fritsch) indicate that R-R interval responses to the neck pressure sequence we used are not reduced by β-adrenergic blockade but are nearly abolished by muscarinic blockade. Therefore, our study focuses primarily on the vagal limb of the baroreceptor reflex.

Plasma measurements. Resting plasma volume was measured on C4, BR3, BR12, and BR25 with an Evans blue dye technique and was determined on R2 from changes in hematocrit and hemoglobin concentrations (14). Resting norepinephrine and epinephrine were measured on C4, BR1, BR12, BR25, and R1 with a radioenzymatic assay (26).

Posture tests. Posture tests were conducted before bed

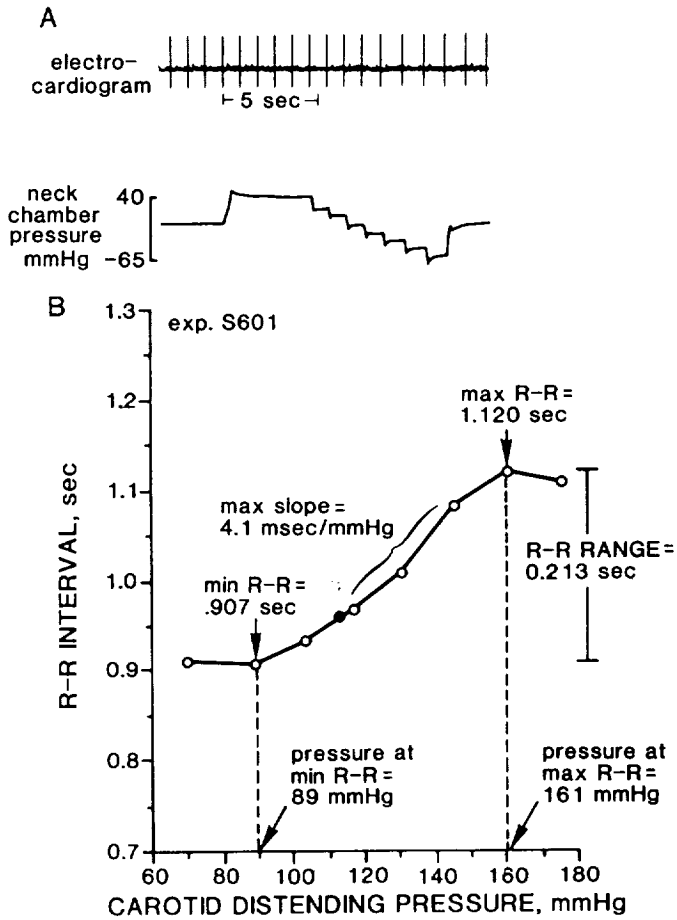

FIG. 1. Experimental record (*A*) and average response of 1 subject to 7 neck pressure sequences (*B*). *B*: parameters of baroreflex relationship used for analysis. Carotid distending pressure was considered to be systolic pressure minus neck chamber pressure. In this subject, steepest slope lay between the 4th and 6th points on relationship. ●, Position of operational point (base-line R-R interval).

[1] We measured carotid baroreceptor stimulus-sinus node response relationships on two occasions in 27 healthy subjects. The first relationship was virtually identical to the second, which was obtained 7–10 days later. Both maximum slopes and R-R interval ranges were comparable on the two occasions. Slopes averaged 5.7 ± 0.8 and 5.7 ± 0.7 ms/mmHg ($P = 0.93$, paired t test) and R-R interval ranges averaged 199 ± 21 and 210 ± 17 ms ($P = 0.36$).

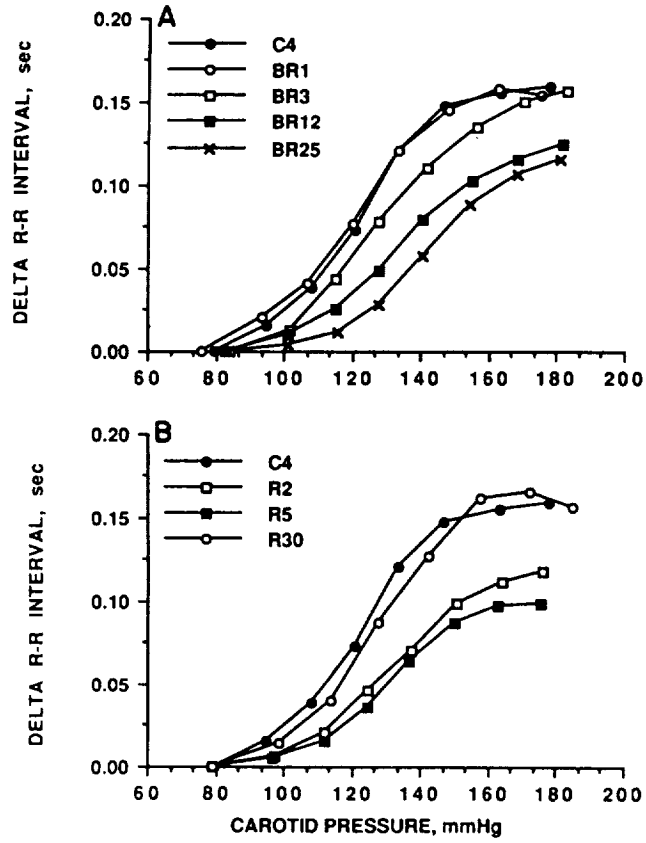

FIG. 2. Carotid baroreceptor-cardiac reflex response relationships. *A*: relationships generated on *days 1, 3, 12,* and *25* of bed rest (BR) and control day before bed rest (C4). *B*: relationships generated on *days 2, 5,* and *30* of ambulatory recovery after bed rest (R) and C4.

rest and immediately on the termination of the 30-day bed rest (R1). Posture tests before and after bed rest began with the subject lying supine for 60 min; this was followed with the subject sitting in bed with his feet hanging over the side of the bed not touching the floor for an additional 60 min. Immediately after the sitting test at the end of bed rest, subjects underwent a 5-min active stand test. The subjects were instructed to stand still with their feet placed 12 in. apart with their weight evenly distributed and to refrain from moving. Thus, contractions of the leg muscles were those required to support stationary standing. Blood pressure and heart rate were measured at the end of *minutes 3* and *5* of standing. Because heart rate is a physiologically important variable, we characterized cardiac responses to standing with heart rates rather than R-R intervals. In all cases, these heart rate values represented the peak heart rate achieved during standing. At the beginning of each test, a butterfly needle was inserted into an antecubital vein. Venous blood samples were drawn before sitting and at 5, 15, and 60 min after sitting in posture tests both before and after bed rest for the determination of norepinephrine and epinephrine. Blood samples were not drawn during standing.

Analysis of baroreflex responses. Previous studies using similar techniques have shown that intrasubject variability is so great that a meaningful fit to a four-parameter logistic equation is not possible for many subjects (13, 16). Therefore, baroreflex relationships were reduced to the following parameters for statistical comparisons: range of R-R interval responses, maximum and minimum R-R interval responses, maximum slope, position of operational point [(control R-R − minimum R-R)/range] × 100%, and carotid distending pressures at minimum and maximum R-R intervals and at maximum slopes. Maximum slopes were determined by application of least-squares linear regression analysis to every set of three consecutive points on the response relationship to find the segment with the steepest slope. The carotid distending pressure at maximum slope was the point halfway between the pressures bracketing the maximum slope. These parameters are illustrated in Fig. 1*B*.

Statistics. Since baroreflex data for all subjects were found to be normally distributed with the Shapiro-Wilk normality test (28), parametric statistical analyses were used. A repeated-measures analysis of variance (ANOVA) technique with contrasts was carried out (25) to determine differences between measurements during the control and experimental sessions. Correlations were sought with least-squares regression (20). Syncopal and nonsyncopal groups were compared with Wilcoxon's rank sum test (1). A two-way ANOVA with days as the factor and subjects as the block was used to determine differences in resting levels of norepinephrine and epinephrine across days. Bonferroni's multiple comparisons

TABLE 1. *Resting blood pressures, catecholamines, plasma volume, and characteristics of the carotid-cardiac baroreflex response before, during, and after bed rest*

	C4	BR1	BR3	BR12	BR25	R2	R5	R30
SBP, mmHg	118±2	115±3	121±3	121±3	122±2	118±4	118±3	120±4
DBP, mmHg	75±3	76±2	73±2	73±2	72±2	78±3	74±2	77±2
MAP, mmHg	89±2	89±2	89±2	89±1	88±1	91±3	89±2	91±2
Base-line R-R interval, s	0.930±0.039	1.021±0.046*	0.894±0.032	0.882±0.032*	0.828±0.031*	0.802±0.033*	0.810±0.027*	0.862±0.021†
Min R-R interval, s	0.893±0.039	0.960±0.045*	0.845±0.031	0.833±0.027*	0.786±0.027*	0.748±0.029*	0.776±0.028*	0.791±0.031†
Max R-R interval, s	1.058±0.052	1.126±0.055*	1.006±0.051	0.963±0.039*	0.908±0.040*	0.870±0.037*	0.880±0.036*	0.958±0.024
R-R interval range, s	0.165±0.02	0.166±0.02	0.161±0.02	0.130±0.02†	0.122±0.02*	0.122±0.02*	0.104±0.02*	0.167±0.02
Max slope, ms/mmHg	3.65±0.64	3.47±0.57	3.25±0.52	2.52±0.35†	2.52±0.33*	2.28±0.34*	2.65±0.60*	3.09±0.52
Max slope, bpm/mmHg	−0.227±0.024	−0.223±0.029	−0.214±0.025	−0.168±0.019*	−0.161±0.025*	−0.188±0.025*	−0.170±0.023*	−0.229±0.039
CDP at max slope, mmHg	127±4	121±4	133±4	129±5	139±6	136±5	136±4	131±6
CDP at max R-R interval, mmHg	165±5	168±7	175±6	174±8	164±9	172±3	172±5	173±7
CDP at min R-R interval, mmHg	85±4	81±5	90±4	93±8	95±6	82±3	86±5	88±6
Norepinephrine, pg/ml	184±21	216±23		148±18	171±17	224±24		
Epinephrine, pg/ml	92±25	72±14		66±17	63±8	72±12		
Plasma volume, ml	3,676±163		3,237±82*	3,140±96*	3,108±98*	3,509±109‡		

Values are means ± SE. SBP and DBP, systolic and diastolic blood pressure; MAP and CDP, mean arterial and carotid distending pressure; C, BR, and R, before, during, and after bed rest, respectively. * $P < 0.05$ vs. C4 value; † $P \leq 0.06$ vs. C4 value. ‡ Calculated from hematocrit and hemoglobin values from C4 and R1.

were used when any factor differences occurred. A three-way ANOVA using test days (before and after bed rest), posture (supine and sitting), and subjects as factors was used to determine differences in the responses of norepinephrine and epinephrine during the posture tests. Subjects were used as a block to absorb any variability between the subjects. Dunnett's multiple comparison was used when any factor differences occurred.

RESULTS

Baroreflex responses. Average baroreflex response relationships for all subjects are depicted in Fig. 2 and are listed in Table 1. These relationships demonstrate that both maximum slopes and ranges of responses decreased progressively with continuing bed rest (Fig. 2*A*) and did not return to base-line values by the 5th day of recovery (Fig. 2*B*). The response relationship shifted significantly on the R-R interval axis but did not shift on the pressure axis (Table 1). There were parallel shifts in base-line, minimum, and maximum R-R intervals. All increased (slightly) after the initial 2 h of bed rest (BR1), progressively decreased through R2, and did not recover by R5. Resting systolic, diastolic, and mean arterial pressures, as well as the carotid distending pressures at minimum and maximum R-R intervals, and maximum slope did not change with bed rest. The position of the operational point was 21.6 ± 8.0% before bed rest and was not altered significantly by bed rest.

Catecholamine responses. Compared with C4, resting norepinephrine and epinephrine levels were not significantly altered during bed rest (Table 1). The elevation of norepinephrine levels induced by the change from supine to sitting positions was significant but did not differ between posture sitting tests before and after bed rest (Fig. 3). There was no change of epinephrine levels during the posture test either before or after bed rest.

Orthostatic responses. Complete data from the stand test were obtained for 10 subjects. Four subjects experienced syncope or presyncope, and the remaining six subjects tolerated the posture test with no noticeable difficulty. Although heart rate increased with standing in both syncopal (23 ± 5 beats/min) and nonsyncopal (+49 ± 10 beats/min) subjects, the increase was significantly less ($P < 0.05$) in the syncopal group (Fig. 4*A*). Nonsyncopal subjects maintained the same systolic pressure before and after bed rest, but syncopal subjects experienced significant reductions of systolic pressures (Fig. 4*B*). Average standing diastolic pressure after bed rest was increased relative to pressure before bed rest ($P < 0.05$), but there was no difference in this response between syncopal and nonsyncopal subjects.

Figure 5 demonstrates that the attenuation of the baroreflex response relationship was less in nonsyncopal (*A*) than in syncopal (*B*) subjects. The reduction in maximum slope of the response relationship from 4.0 to 2.2 ms/mmHg for the syncopal group was significantly greater ($P = 0.042$) than the reduction from 3.1 to 2.7 ms/mmHg in the nonsyncopal group (Fig. 6*A*). The change in the maximum slope of the baroreflex response relationship from C4 to BR25 correlated ($r = 0.70$, $P = 0.030$) with the change in systolic pressure from supine

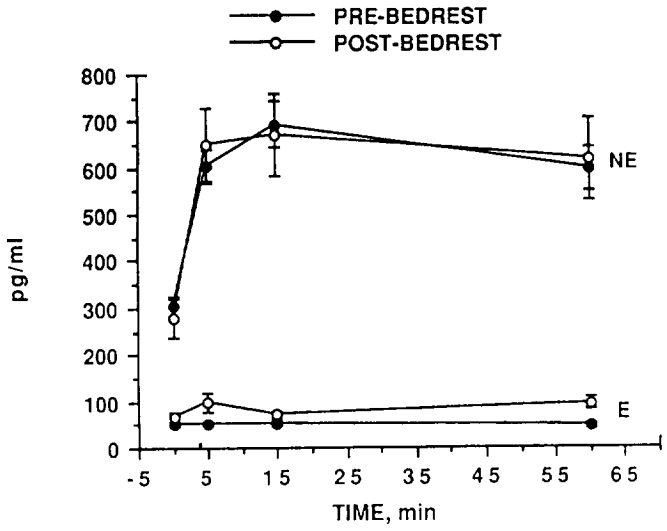

FIG. 3. Plasma concentrations of norepinephrine (NE) and epinephrine (E) during supine rest (time = 0 min) and at 5, 15, and 60 min of sitting before and after bed rest.

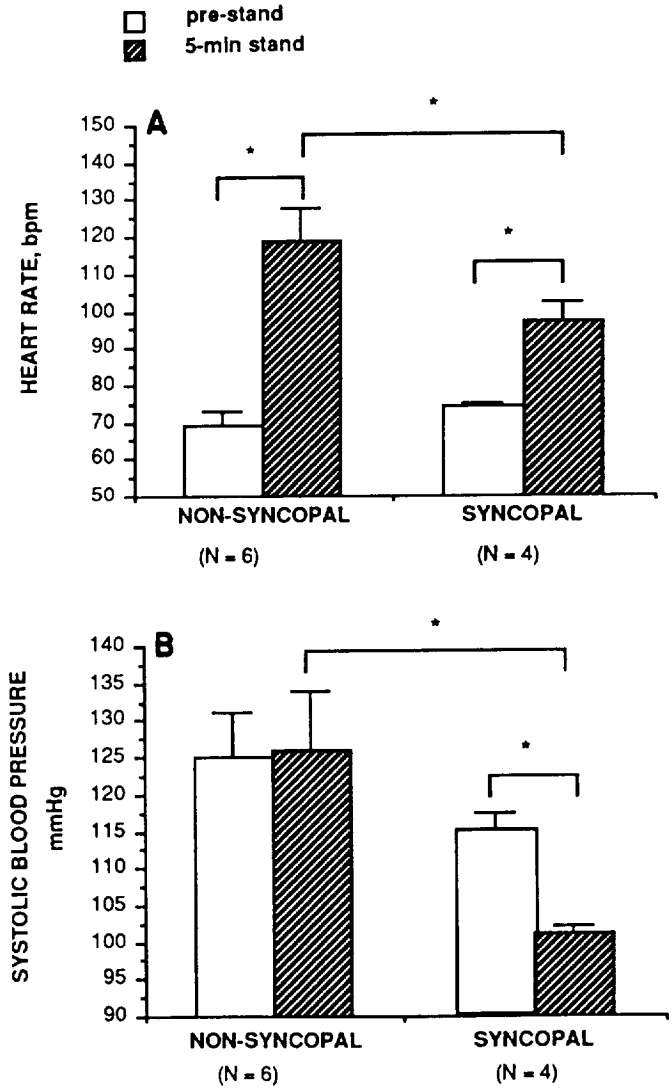

FIG. 4. Heart rate (*A*) and systolic blood pressure (*B*) during supine rest (pre-stand) and at 5 min of standing in nonsyncopal and syncopal subjects after bed rest. *Differences at $P < 0.05$.

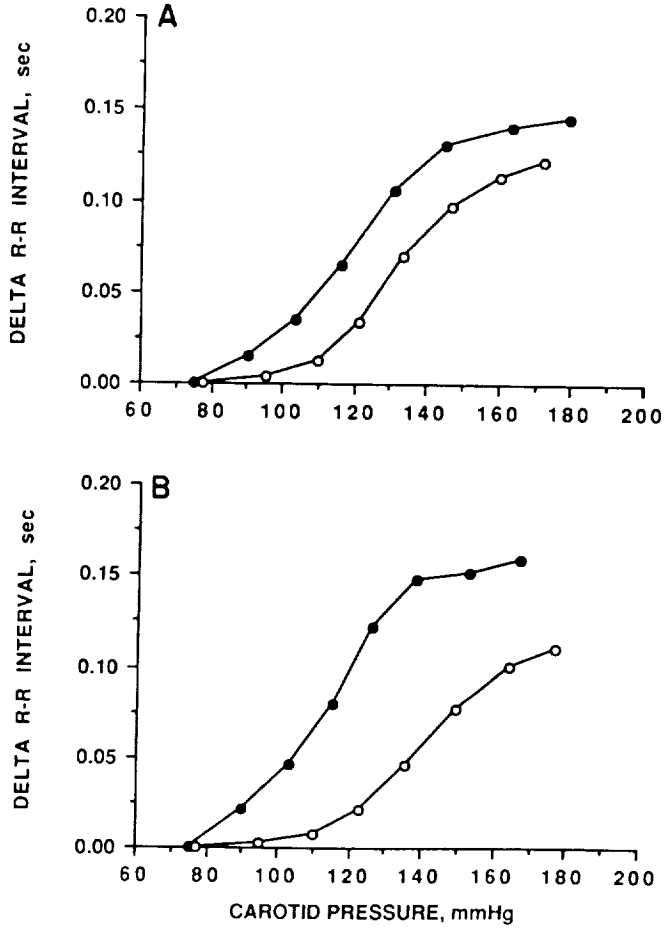

FIG. 5. Carotid baroreceptor-cardiac reflex before (●) and at the end (○) of bed rest in nonsyncopal (*A*) and syncopal (*B*) subjects.

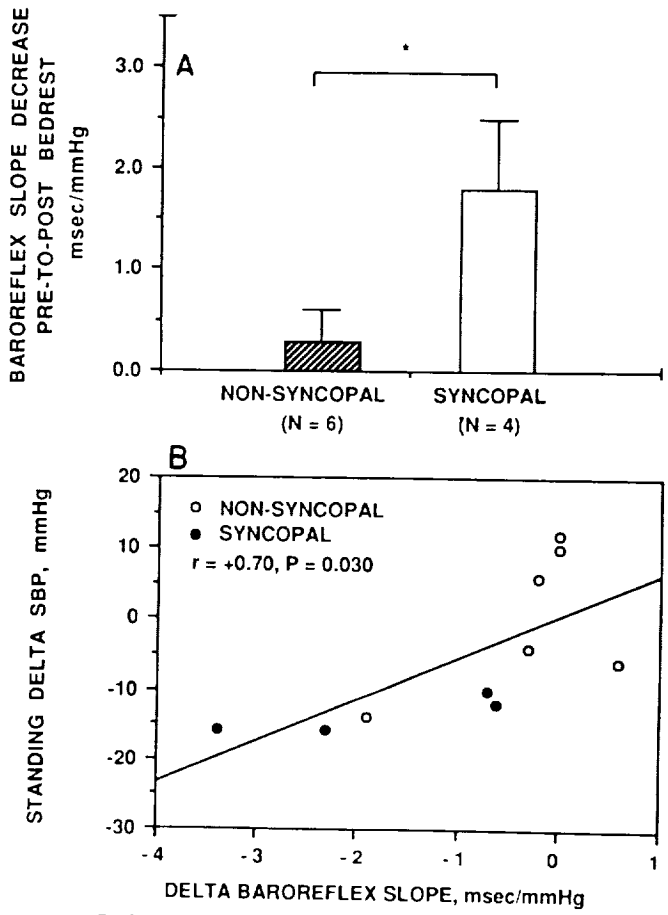

FIG. 6. Reduction in maximum slope of carotid baroreceptor-cardiac reflex relationship after bed rest in nonsyncopal and syncopal subjects (*A*) and relationship between change in maximum slope and change in systolic blood pressure (SBP) during stand test after bed rest (*B*). *Differences at $P < 0.05$.

to standing during the posture test before bed rest (Fig. 6*B*).

Plasma volume responses. Mean resting plasma volume for all subjects decreased by ~15% by BR3 but showed no further reduction through the end of bed rest (Table 1). An estimate of resting plasma volume calculated from hematocrit and hemoglobin levels at C4 and R1 indicated a rapid return to levels before bed rest by the 1st day of ambulation. Reductions ($P < 0.05$) of plasma volume, from 47.3 ± 2.6 ml/kg on C4 to 40.1 ± 1.7 on BR25 in nonsyncopal subjects, were not significantly different from those of syncopal subjects (whose average reduction of plasma volume, from 46.4 ± 1.5 to 42.6 ± 1.7 ml/kg, was actually less). There was no significant correlation between changes of plasma volume during bed rest and changes of baroreflex slopes ($r = -0.17$, $P = 0.376$).

DISCUSSION

We measured vagally mediated carotid baroreceptor-cardiac reflex responses in 11 healthy men before, during, and after 30 days of 6° head-down bed rest to test the hypothesis that baroreflex malfunction contributes to the orthostatic hypotension associated with this model of simulated microgravity. The major findings of this study are that head-down bed rest leads to substantial and progressive impairment of baroreflex function and that the development of baroreflex malfunction is related significantly to the occurrence of hypotension during standing after bed rest. Our data may be the first to demonstrate in healthy humans that impairment of baroreflex function can be provoked experimentally, is associated with clinical symptoms, and can be reversed completely.

Vagal responses. Sigmoidal baroreceptor-cardiac reflex relationships shifted on the R-R interval axis during bed rest (Table 1). Average base-line R-R intervals increased after 2 h of bed rest and then declined progressively during the bed rest period. Baroreflex changes became significant by BR12 and persisted through at least 5 days of ambulatory recovery. Some of our results confirm those of Billman et al. (2), who reported that primates experience reductions of R-R interval prolongation after phenylephrine injections, between *days 7* and *28* of horizontal body casting.

We chose R-R intervals to express cardiac responses to carotid stimulation because of their linear relationships to vagal-cardiac nerve activity (17, 21). Rowell (22) demonstrated that elevations in base-line heart rate of 40–120 beats/min during exercise result in reduced baroreflex sensitivity when the slope is based on the R-R interval-blood pressure relationship; however, the baroreflex slope is unaltered when expressed by the heart rate-blood pressure relationship. This controversy raises an issue of whether the reduced maximum slope of the

baroreflex response in our bed rest subjects might have resulted from their increased resting base-line heart rates. We therefore calculated maximum slopes of the carotid-cardiac baroreflex using both measured R-R interval and calculated heart rate. Despite changes in base-line R-R intervals during bed rest, the reduction in maximum slope of the baroreflex relationship during bed rest was established using both expressions of cardiac responses (Table 1). Thus a change in resting heart rate of ≤10 beats/min in the present study did not have an effect on the calculated maximum slope of the stimulus-response relationship of the carotid-cardiac baroreflex.

Increases and reductions of gain and maximum and minimum R-R intervals during carotid baroreceptor stimulation tended to occur in parallel with elevations and reductions of base-line R-R intervals. This relationship raises the issue that increasing resting heart rate may alter the baroreflex response. Our data do not explain this relationship. However, compared with C4, the base-line R-R interval was significantly elevated on BR1 and R30 without significant changes in baroreflex slope. Furthermore, different studies that involved serial measurement of baroreflex responses in the same subjects during circadian changes in base-line heart rate (16) and over 10 wk of exercise training (9) have documented acute and chronic alterations in base-line R-R intervals without changes in reflex gain. It therefore appears unlikely that changes in base-line R-R interval could explain the reductions in baroreflex slope observed in our subjects.

Progressive baroreflex shifts were not associated with alterations of resting systolic, diastolic, or mean arterial pressures or the carotid distending pressures that elicited minimum and maximum R-R interval responses (near baroreceptor threshold and saturation). However, there was impairment of subjects' capacities to respond to and compensate for changes of blood pressure during standing. Our finding that impairment of vagally mediated baroreflex responses may be associated with impaired blood pressure regulation but unchanged resting blood pressure is not without precedent. Conway et al. (10) and Watson et al. (29) showed that, in hypertensive patients, impairment of vagally mediated baroreflex responses (abrupt R-R interval prolongations after blood pressure elevations provoked by bolus injections of phenylephrine) is associated with increased variability of arterial pressure. Cowley et al. (11) reported that, in conscious dogs, sinoaortic denervation (an extreme form of baroreflex impairment) is associated with supranormal blood pressure variability during upright posture. Our data are consistent with these earlier observations and support the idea that the primary function of baroreflexes may not be to set chronic levels of arterial blood pressure but to buffer transients in blood pressure, including those caused by postural changes.

Blood volume changes. One mechanism that may be responsible for our findings is impairment of baroreflex control by blood volume reductions. Harrison et al. (15) suggested that central blood volume changes alter carotid baroreflex responses, because head-down tilt reduces and head-up tilt increases R-R responses to neck pressure stimuli. In our study, the time courses of changes in plasma volume and slope of the baroreflex relationship were not parallel. Plasma volume fell significantly by the 3rd day of bed rest, at a time when maximum slope of the baroreflex response relationship had not changed. After the initial 3 days of bed rest, plasma volume remained at constant low levels for the remainder of bed rest, but maximum baroreflex slopes declined progressively between *days 12* and *25*. Plasma volume was restored to control levels within the 1st day of ambulation after bed rest, but maximum baroreflex slopes remained depressed for at least 5 days after bed rest. Thus, although our data do not rule out a contribution from reduced blood volume, they point away from reductions of blood volume as the sole cause of the baroreflex abnormalities that developed during bed rest.

Sympathetic responses. Against expectations, there was no evidence for reciprocal impairment of sympathetic responses; catecholamine levels were comparable in lying and sitting positions before and after bed rest (Fig. 3). We used antecubital vein plasma norepinephrine levels as indexes of sympathetic nerve activity, because they are related closely to baroreflex-mediated changes of muscle sympathetic nerve activity (12). Although we measured catecholamines in lying and sitting positions, we did not measure catecholamine levels during standing. Burke et al. (5) found that muscle sympathetic nerve activity increased when subjects changed from lying supine to sitting and increased further when they stood. Thus our data on sympathetic mechanisms are limited and do not exclude an abnormality of reflex sympathetic neural control. Such an abnormality might be expected on the basis that both vasoconstriction and cardioacceleration (19) during prolonged standing result importantly from increased sympathetic outflow.

Orthostatic hypotension. A subgroup of four subjects became syncopal during 5 min of standing after bed rest. Compared with subjects who tolerated upright posture well after bed rest, syncopal subjects demonstrated an inability to increase heart rates adequately, despite a greater unloading of baroreceptors (i.e., a greater reduction of systolic blood pressure, see Fig. 4). Although other factors, such as reduced circulating blood volume (3, 6), increased leg vascular compliance (18), and reduced responses of vasoactive hormones (3, 6, 24), may have contributed to orthostatic intolerance, there were no significant differences in blood volume reductions and catecholamine responses between syncopal and nonsyncopal subjects. Significant elevations in average calf compliance from before and after bed rest, which have been reported for these subjects (8), did not differ between syncopal (4.0 ± 1.3 to 5.3 ± 0.9 vol%/mmHg) and nonsyncopal (4.0 ± 0.5 to 5.1 ± 0.7 vol%/mmHg) subjects.

Syncopal subjects demonstrated greater reductions in maximum slope and buffer capacity (range of R-R interval change) of their baroreflex response relationship than nonsyncopal subjects. The degree of impairment of baroreflex function after bed rest correlated directly with the greater reduction in systolic blood pressure (Fig. 5*B*) and the smaller tachycardia during standing. Our data may be related to those of Cowley et al. (11), who found that conscious dogs with sinoaortic baroreceptor denervation had smaller heart rate increases and greater blood

pressure reductions during upright posture than dogs with intact baroreflexes.

Although our results do not prove that baroreflex abnormalities cause orthostatic hypotension after head-down bed rest, they support such a notion and raise the intriguing possibility that baroreflex impairment contributes to the orthostatic hypotension experienced by astronauts after spaceflight. Most US astronauts experience symptoms of lightheadedness, and some progress to presyncope or syncope during standing after spaceflights of 7–10 days (3). We hypothesize that as the duration of spaceflight increases, progressive attenuation of baroreceptor-cardiac responses occurs and leads to greater postflight orthostatic intolerance. If this hypothesis is validated, development of effective countermeasures for postflight orthostatic hypotension following projected 90- to 180-day Space Station missions might include techniques to increase vagal-cardiac activity and baroreflex responsiveness before reentry.

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